

University of Groningen

Studies in ovarian cancer of factors related to prognosis, tumor growth and aggressiveness

Arts, Henriëtte Johanna Gertruda

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

2002

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Arts, H. J. G. (2002). Studies in ovarian cancer of factors related to prognosis, tumor growth and aggressiveness. Groningen: s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Summary

Despite the introduction of relatively new antineoplastic drugs such as paclitaxel and topotecan in the treatment of advanced ovarian carcinoma, there remains a high percentage of patients who cannot be cured. Intrinsic or acquired resistance to currently available cytotoxic agents is the major obstacle in the treatment of patients with advanced ovarian carcinoma. Increasing the drug dose by e.g. intraperitoneal treatment has a limited additional effect. Therefore, more insight into the cellular mechanisms responsible for both drug response and drug resistance should help to develop more effective treatment methods. In this thesis several studies in ovarian cancer are described, which focus on factors related to drug response and prognosis.

Chapter 1 reviews the available data on clinicopathologic prognostic factors in ovarian cancer and on cell biological parameters involved in drug resistance and apoptosis. Currently, the only factors which influence treatment decisions are the classic prognostic factors. The most important prognostic factor is FIGO stage of disease at diagnosis. Additional prognostic value can be attributed to the presence of residual tumor after first laparotomy, clinical performance status, age and tumor differentiation grade. However, these factors are poor predictors of the tumor response to chemotherapy. *In vitro* studies have identified numerous factors which determine the chemosensitivity of tumor cells. "Classic" concepts of resistance to cytotoxic drugs are related to the inability of drugs to reach the intracellular target, enhanced efflux of drugs, increased detoxification of active drugs, enhanced DNA repair or increased tolerance to DNA crosslinks. Especially multidrug resistance (conferred by amongst others, the membrane transporter proteins P-gp and MRP1) has extensively been studied. *In vitro*, there is a strong relation between these proteins and the emergence of drug resistance. So far, however, it has been difficult to translate these *in vitro* data into clinical practice. Furthermore, strategies aimed at reversal of these resistance mechanisms did not yet result in a treatment advantage for patients with solid tumors.

It is becoming increasingly apparent that conventional cytotoxic drugs exert their effect by the cellular machinery that controls the cell cycle and the molecular pathways that mediate programmed cell death or apoptosis.¹ Suppression of drug-induced apoptosis is considered to be a general mechanism for drug resistance of tumor cells. The p53 tumor suppressor protein plays a key role in coordinating this process. Mutations in the p53 gene occur in over 50% of human ovarian carcinomas and have been associated with shorter survival. Numerous other proteins have been identified, which play a role in the apoptotic response, such as the members of the BCL-2 family and the death transmembrane receptors and their ligands, TNF α , FasL and TRAIL.

The recent development of methodologies that allows the assessment of changes in global gene expression in tumors will facilitate the high throughput evaluation for clinical significance of all cell biological factors that *in vitro* have been shown to be involved in response to therapy. Application of cDNA microarrays allows simultaneous determination of expression levels of thousands of mRNAs of tissue samples or cell lines and comparison of global gene expression patterns in drug resistance and sensitivity in primary tumor cell populations, thereby generating multiple clues to which (unknown) gene(cluster)s are involved in drug response. At the end of chapter 1 several novel therapeutic strategies, based on cell biologic aberrations that are specific in certain malignancies, such as the use of agents aimed at restoration of the apoptotic machinery of the cell, are discussed.

Intraperitoneal administration of cytotoxic drugs is one of the more "classic" treatment modifications, aimed to establish very high local drug concentrations. In **chapter 2**, we describe our experience with the laparoscopic placement of peritoneal access ports, compared

to the experience with placement by laparotomy. All patients were enrolled in a study to receive intraperitoneal paclitaxel in combination with intravenous carboplatin and cyclophosphamide as first- or second-line chemotherapy for ovarian carcinoma stage III/IV. The patients had a peritoneal access port (PAP-catheter) placed subcutaneously at primary laparotomy or by a separate laparoscopic procedure under general anesthesia. PAP-catheter placement during laparotomy was possible in all 13 patients without complications. Thirteen patients had laparoscopic catheter placement, using routine Veress needle insufflation. When one patient experienced a bowel perforation at insertion of the umbilical trocar, due to extensive adhesions, we decided to continue with an open laparoscopic procedure. No other procedure or catheter-related complications occurred. Therefore, laparoscopic assisted placement of PAP-catheters is feasible, but should preferably be performed by an open laparoscopic procedure in this patient population at risk for intraabdominal adhesions.

In **chapter 3**, the prognostic value is studied of the drug resistance associated proteins P-glycoprotein (P-gp), Multidrug Resistance associated Protein (MRP1), canalicular Multispecific Organic Anion Transporter (c-MOAT/MRP2) and the Lung Resistance Protein (LRP) in ovarian carcinoma. The expression of P-gp, MRP1, MRP2 and LRP was determined by immunohistochemistry on frozen tissue sections of 115 ovarian carcinoma patients and related to clinicopathological factors, response to chemotherapy and progression free and overall survival. Expression of P-gp was observed in 17%, MRP1 in 44%, MRP2 in 16% and LRP in 74% of the tumors. Expression of MRP1 was related to MRP2 and P-gp expression, while LRP expression was more frequently observed in patients with more favorable tumor characteristics, such as early stage, low grade and smaller residual tumor. P-gp, MRP1, MRP2 and LRP expression were neither related to response to first line chemotherapy nor to progression free or overall survival. In the multivariate analysis only stage and residual tumor were independent prognostic factors for survival. Thus, assessment of P-gp, MRP1, MRP2 or LRP does not allow prediction of response to chemotherapy or survival in ovarian carcinoma.

Heat shock protein 27 (hsp27) is one of the small heat shock proteins. The highly conserved heat shock proteins accumulate in cells exposed to heat and a variety of other stressful stimuli. They function mainly as molecular chaperones, allowing cells to adapt to gradual changes in their environment and to survive in otherwise lethal conditions. In ovarian and breast carcinoma cell lines, the expression of hsp27 has been associated with resistance to cisplatin and doxorubicin. In addition hsp27 expression appears to facilitate cellular growth, differentiation and motility.² Recently it has been shown that expression of heat shock proteins correlates with increased resistance to apoptosis induced by a range of diverse cytotoxic agents.³ In several human carcinomas hsp27 expression has also been related to worse prognosis.⁴

In **chapter 4**, the prognostic value of hsp27 expression is studied in patients with ovarian carcinoma with respect to their response to chemotherapy and overall survival. Hsp27 expression was assessed by immunohistochemistry in 77 patients with ovarian carcinoma stage IC-IV. All patients received cisplatin and doxorubicin-based chemotherapy and there was a long-term follow-up. In 30 patients paired tumor samples, obtained before and after chemotherapy, were available. Hsp27 immunostaining was positive in 86% of patients before and in 72% of patients after chemotherapy. Hsp 27 expression was not related to any clinicopathologic factor or p53 expression. Univariate analysis showed that in stage III and IV ovarian cancer patients younger age, no residual tumor after first laparotomy, ≤ 1 liter ascites, response to first line chemotherapy and absence of hsp27 expression were associated with longer median progression-free survival. However, in multivariate analysis only age, ascites and response to chemotherapy had independent prognostic value.

In **chapter**
The Fas-F
and atresia
involved in
normal me
with benign
evaluated
was also d
comparabl
were high
Epithelial
malignant
epithelium
serum Fas
ovarian ca
production
ovarian tur
innovative

Wild-type
in transact
carcinoma
three vecto
codon 273
expression
Fas levels,
surface (10
the cell line
levels beca
cisplatin (3
increased a
insensitive
interferon-
percentage
levels indu
combination
following i
status of ov
percentage
Fas antibod
patients wit
success of l
in mice.

Recently, T
various typ
receptors, d
2 (DcR1 an
tumor selec
carcinomas

In **chapter 5**, the components of a specific apoptotic pathway are studied in ovarian tumors. The Fas-Fas ligand (FasL) route appears to be involved in the physiology of follicular growth and atresia of normal ovaries.⁵ Furthermore it has been shown that this apoptotic route is also involved in the process of regeneration and atresia of the epithelial ovarian surface cells in the normal menstrual cycle.⁶ In this study, Fas and FasL levels in cyst fluids and sera of patients with benign (n=30), borderline (n=5) and malignant (n=24) epithelial ovarian tumors were evaluated by ELISA. The immunohistochemical expression of Fas and FasL in relation to p53 was also determined in the tumors of these patients. In serum, median Fas levels were comparable in healthy women and patients with ovarian tumors, while serum FasL levels were higher in healthy women. The median Fas levels were higher in malignant cyst fluids. Epithelial Fas staining was observed in 46% of benign, 80% of borderline and 71% of malignant tumors, while FasL staining was more frequently present in malignant ovarian epithelium. P53 immunostaining was not related to Fas or FasL expression. In conclusion, serum Fas or FasL level measurements do not seem to be useful markers in patients with ovarian carcinomas. Elevated Fas levels in malignant cyst fluids, suggest an increased production of Fas by malignant cells. As both Fas and FasL are highly expressed in malignant ovarian tumors, the Fas-FasL route appears an interesting apoptotic route to explore for innovative cancer therapy.

Wild-type p53 has been implicated in the translocation process of Fas to the cell surface and in transactivation of the Fas gene.⁷ The p53 gene, however, is frequently mutated in ovarian carcinoma. In **chapter 6**, stable transfectants expressing the control vector (A2780/cmv), and three vectors with p53 mutated at codon 175 (A2780/m175), codon 248 (A2780m248) or codon 273 (A2780/m273) were used to determine the effect of various p53 mutations on Fas expression and Fas-mediated cytotoxicity in an isogenic background. Despite similar cellular Fas levels, the cell lines A2780/m248 and A2780/m273 expressed more Fas on the cell surface (10- and 5- fold respectively) compared to A2780/cmv and A2780/m175, but none of the cell lines was sensitive for the apoptosis-inducing anti-Fas antibody 7C11. Fas cell-surface levels became elevated in all cell lines following treatment with interferon- γ (2 to 3-fold), cisplatin (3 to 5-fold) or paclitaxel (1.3 fold). These elevated Fas cell surface levels resulted in increased apoptosis following anti-Fas antibody 7C11 exposure. Especially A2780/m248, insensitive to either 7C11 or interferon- γ , was highly sensitive to a combination of 7C11 and interferon- γ . This sensitivity was demonstrated by an increase in PARP cleavage, in the percentage apoptotic cells, and in percentual cell kill. In contrast, the high Fas cell surface levels induced by cisplatin did not result in an enhanced cytotoxic effect of cisplatin in combination with 7C11. These results demonstrate that upregulation of Fas on the cell surface following interferon- γ treatment may be used to enhance cell kill independently of the p53 status of ovarian tumor cells. This also indicates that, despite the occurrence of a high percentage of p53 mutations, especially the combination treatment of interferon- γ and an anti-Fas antibody might enhance the efficiency of current platinum-based chemotherapy for patients with ovarian carcinoma. However, a significant problem that could hamper the success of FasL as therapeutic agent, is the severe hepatotoxicity of FasL, as was encountered in mice.

Recently, TRAIL, a member of the TNF cytokine family, that triggers rapid apoptosis in various types of tumor cells has drawn more attention.⁸ TRAIL can interact with two death receptors, death receptor 4 and 5 (DR4 and 5) and two decoy receptors, decoy receptor 1 and 2 (DcR1 and DcR2). In contrast to TNF α and FasL, cytotoxicity to TRAIL appears to be tumor selective, thereby making TRAIL a more promising new candidate for the treatment of carcinomas. Until now however, little is known about the expression of TRAIL and its

receptors in human carcinomas. Therefore, in **chapter 7**, the expression of the death ligand TRAIL and its death receptors DR4 and DR5 and DcR1 is studied by immunohistochemistry in normal ovaries and in patients with early or advanced stage ovarian carcinoma. In the latter group, tissue was available at diagnosis and at second look laparotomy, performed after three or six cycles of chemotherapy, allowing the study of potential induction of TRAIL and its receptors by exposure to chemotherapy.

In normal ovaries immunostaining for TRAIL, DR4 and DR5 was observed only in the cytoplasm of ovarian surface epithelium, whereas immunostaining for DcR1 also was observed in the ovarian stromal cells. Immunostaining for TRAIL was observed in 34%, DR5 in 51%, DR4 in 71% and DcR1 in 44% of the primary tumors. Eighty eight percent of the tumors was positive for at least one death receptor. All staining patterns were cytoplasmatic and within a tumor generally weaker in undifferentiated parts of the tumor. TRAIL was more frequently expressed in early stage tumors, compared to advanced stage tumors. No other correlations of TRAIL, DR4, DR5 and DcR1 with any clinicopathological characteristic were found. Also no relations were observed with response to chemotherapy or survival (in this small group of patients). DR5 was more frequently observed in residual tumors after chemotherapy than before chemotherapy. This is in line with *in vitro* results in other tumor types, where especially DR5 upregulation (and enhanced cytotoxicity to TRAIL) is observed upon treatment of tumor cells with cytotoxic drugs. As early, advanced and relapsed tumors all show high expression of at least DR4 or DR5, the clinical use of recombinant human TRAIL is a potentially interesting therapeutic option to explore in ovarian carcinoma, especially in drug resistant tumors.

General discussion and future perspectives

Although 80% of patients with advanced ovarian carcinoma respond to first-line treatment, the majority will eventually relapse. Response rates to a variety of agents shown to be effective as second line treatment all range from 20-30% and will seldom be curative. The identification of relevant prognostic factors in ovarian carcinoma, might provide targets for novel therapeutic strategies.

Although the (multi)drug resistance related proteins P-gp, MRP1, MRP2 and LRP are frequently expressed by ovarian tumors, we showed that their expression is not related to resistance to chemotherapy or to survival. It could be assumed that tumors expressing all four drug resistance associated proteins, would be poor responders to first line chemotherapy. However, based on expression of these drug resistance related proteins, we were unable to identify a subgroup of patients with an unfavorable response to chemotherapy. This might be due to the co-expression of yet unidentified other proteins which act as e.g. drug-efflux pumps. Recently several new drug-efflux pumps have been identified.⁹ The contribution of these new drug-efflux pumps to clinical drug resistance however, remains to be established. Drug-efflux pumps or drug-resistance associated proteins have a physiological role in normal tissues. Clinical studies aimed at reversal of P-glycoprotein have not provided any benefit for patients with solid tumors. It may well be that drug resistance in the clinic is only possible if more than one drug resistance mechanism is attacked.

It is becoming increasingly apparent that conventional chemotherapeutic drugs exert their function ultimately via the cellular machinery that controls the cell cycle and the molecular pathways that mediate programmed cell death or apoptosis. Suppression of drug-induced apoptosis, despite imposition of drug-induced damage, is considered to be a general mechanism for drug resistance of tumor cells. In chapter 5 and 6 different aspects of the Fas-FasL apoptotic route are studied to explore its potential as a possible therapeutic target. In

chapter 5, we show that the majority of ovarian carcinomas express both Fas and FasL. This has also been observed in other studies in ovarian carcinoma. For several other tumor types (esophagus, colon, breast) Fas expression appeared to be downregulated in malignant tumors compared to their benign counterparts, while FasL expression was upregulated. It has been suggested that alterations in the expression of Fas and/or FasL that occur during malignant transformation might render tumor cells resistant to T-cell mediated apoptosis. Our study shows that Fas expression is not downregulated in malignant ovarian tumors but that FasL expression is indeed upregulated in malignant tumors compared to benign and borderline tumors. This was confirmed in a larger study of Munakata et al.¹⁰ In their study FasL positive tumors had a shorter overall survival compared to FasL negative tumors. In cystic fluids of malignant tumors, we observed an increased Fas accumulation, which may point to an increased soluble Fas production by malignant ovarian tumor cells. This may also contribute to a decreased sensitivity of tumor cells to T-cell mediated apoptosis. FasL was not elevated, neither in cystic fluids nor in sera from patients with malignant tumors. The abundant Fas expression in ovarian carcinomas supports the use of anti-Fas or rhFasL as a novel therapeutic strategy. However there remain several problems which could seriously hamper this approach. A lack of Fas cell surface expression will result in relative resistance to Fas-mediated apoptosis. We used immunohistochemistry to study the Fas expression and observed especially a cytoplasmatic staining pattern. Immunohistochemistry however, is not sensitive enough to permit any firm conclusion about the expression of Fas on the cell membrane. Currently no data exists on the functionality of the Fas receptor in ovarian carcinomas. Mutations in the Fas gene have been described in other human carcinomas, although not frequently.

Wild type p53 has been implicated in the process of Fas translocation to the cell surface and in transactivation of the Fas gene, while the p53 gene is frequently mutated in ovarian carcinoma. In our study, described in chapter 6, we show that in stable transfectants of the ovarian carcinoma cell line A2780, expressing either a control vector (A2780/cmv), or vectors mutated at codon 175 (A2780/m175), 248 (A2780/m248) or 273 (A2780/m273), treatment with cisplatin, paclitaxel and interferon- γ results in upregulation of Fas on the cell surface. This upregulation was not restricted to wild-type p53 status. Especially in the A2780/m248, not sensitive to either 7C11 or interferon- γ alone, combination of 7C11 and interferon- γ resulted in enhanced cytotoxicity, accompanied by increased PARP cleavage, increased percentage apoptotic cells and cell kill. Other reports have demonstrated that ovarian carcinoma cells, initially not sensitive for anti-Fas antibody, can be sensitized to anti-Fas antibody by subtoxic concentrations of cisplatin. Although our study showed upregulation of Fas cell surface expression upon treatment with cisplatin, mutant p53 transfected A2780 cells were not very sensitive to anti-Fas antibody treatment following cisplatin exposure. As no mutations in the Fas gene have been found in A2780 or in other human ovarian carcinoma cell lines, this suggests that probably intracellular inhibitors of Fas-mediated apoptosis are involved.¹¹ Thus, upregulation of Fas on the cell surface following treatment with cisplatin or interferon- γ may be used to enhance cell kill independently of the p53 status of ovarian carcinoma cells. However, the existence of different intracellular mechanisms for apoptosis inhibition could present a major problem. Therefore future studies should focus on obtaining more insight into these mechanisms. In this respect, the use of short term cultures of human ovarian carcinoma cells is an interesting model to study the functionality of the Fas/FasL pathway.

Despite the above described obstacles, which theoretically could hamper the success of anticancer treatment with anti-Fas or recombinant FasL, experiments in mice have shown that both anti-Fas antibodies and recombinant FasL are capable to induce tumor regression. Unfortunately systemic delivery of these agents also caused severe damage to the liver of the

mice. There are however, several potential options to avoid or reduce this liver toxicity, such as local intra-tumor administration of anti-Fas or recombinant FasL, gene therapy, or the use of a caspase-9 inhibitor, which may protect liver cells from death receptor-mediated apoptosis.¹²

Although the induction of Fas-mediated apoptosis as anticancer treatment remains an interesting option to explore further, the use of another apoptosis inducing ligand, TRAIL, might be more promising, mainly due to its tumor selectivity. In our immunohistochemical study, we observed frequent expression of the death receptors DR4 and 5 in ovarian carcinomas. Interestingly, expression of DR5 was even more frequent in tumor samples obtained after chemotherapy compared to primary tumor samples. This corresponds with *in vitro* results which also show predominantly upregulation of DR5 upon exposure of tumor cell lines to chemotherapy. This increase is *in vitro* accompanied by an increased sensitivity to TRAIL. It is tempting to speculate that the observed increased expression of DR5 in our study, also points to a potential increase in cytotoxicity of chemotherapy if combined with TRAIL. We observed a lower TRAIL expression in advanced stage ovarian carcinomas compared to early stage carcinomas. If confirmed in a larger series, this depletion of TRAIL in advanced stage carcinomas would provide an even further support for the administration of TRAIL as antitumor therapy in advanced ovarian carcinoma.

In conclusion, although in the last decades our knowledge of the cellular events that play a role in resistance to chemotherapy has increased tremendously, this has not yet resulted in a treatment advantage for patients with advanced ovarian carcinoma. So far, most studies evaluated only one or two separate cell biological parameters, while it is obvious that clinical drug resistance is multifactorial and far more complex than previously assumed. Recent advances in methodology for simultaneous analysis of differential gene expression patterns allow for the determination of expression levels of thousands of different mRNAs of tissue samples. The use of cDNA micro-arrays for the comparison of global gene expression patterns in drug resistant and sensitive primary tumor cell populations will identify many more potential molecular markers that contribute to the response of a tumor to chemotherapy. This should result in stratification, aimed at targeting several different molecular markers simultaneously and reveal the right target in the right patient.

References

1. Fisher DE, A
2. Oesterreich S, protein hsp2
Cancer Res
3. Creagh EM, cells. Leukem
4. Arts HJ, Hol Heat-shock-p
chemotherap
5. Hakuno N, K system as a n
137: 1938-48
6. Quirk SM, C cells. Endocr
7. El-Deiry WS
8. Wiley SR, Sc Rauch C, Sm
TNF family t
9. Borst P, Ever associated pro
10. Munakata S, Fas ligand an
neoplasms. B
11. Bertoni F, Co Fas/CD95 ger
12. Ozoren N, Ki LEHD-FMK p
necrosis facto

References

1. Fisher DE. Apoptosis in cancer therapy: crossing the threshold. *Cell* 1994; 78: 539-42.
 2. Oesterreich S, Weng CN, Qiu M, Hilsenbeck SG, Osborne CK, Fuqua SAW. The small heat shock protein hsp27 is correlated with growth and drug resistance in human breast cancer cell lines. *Cancer Res* 1993; 53: 4443-8.
 3. Creagh EM, Sheehan D, Cotter TG. Heat shock proteins—modulators of apoptosis in tumour cells. *Leukemia* 2000; 14: 1161-73.
 4. Arts HJ, Hollema H, Lemstra W, Willemse PH, De Vries EG, Kampinga HH, Van der Zee AG. Heat-shock-protein-27 (hsp27) expression in ovarian carcinoma: relation in response to chemotherapy and prognosis. *Int J Cancer* 1999; 84: 234-8.
 5. Hakuno N, Koji T, Yano T, Kobayashi N, Tsutsumi O, Taketani Y, Nakane PK. Fas/APO-1/CD95 system as a mediator of granulosa cell apoptosis in ovarian follicle atresia. *Endocrinology* 1996; 137: 1938-48.
 6. Quirk SM, Cowan RG, Huber SH. Fas antigen-mediated apoptosis of ovarian surface epithelial cells. *Endocrinology* 1997; 138: 4558-64.
 7. El-Deiry WS. Regulation of p53 downstream genes. *Semin Cancer Biol* 1998; 8: 345-57.
 8. Wiley SR, Schooley K, Smolak PJ, Din WS, Huang CP, Nicholl JK, Sutherland GR, Smith TD, Rauch C, Smith CA, Goodwin RG. Identification and characterization of a new member of the TNF family that induces apoptosis. *Immunity* 1995; 3: 673-682.
 9. Borst P, Evers R, Kool M, Wijnholds J. A family of drug transporters: the multidrug resistance-associated proteins. *J Natl Cancer Inst* 2000; 16: 1295-302.
 10. Munakata S, Enomoto T, Tsujimoto M, Otsuki Y, Miwa H, Kanno H, Aozasa K. Expressions of Fas ligand and other apoptosis-related genes and their prognostic significance in epithelial ovarian neoplasms. *Br J Cancer* 2000; 82: 1446-52.
 11. Bertoni F, Conconi A, Carobbio S, Realini C, Codegoni AM, Zucca E, Cavalli F. Analysis of Fas/CD95 gene somatic mutations in ovarian cancer cell lines. *Int J Cancer* 2000; 86:450.
 12. Ozoren N, Kim K, Burns TF, Dicker DT, Mosconi AD, El-Deiry WS. The caspase 9 inhibitor Z-LEHD-FMK protects human liver cells while permitting death of cancer cells exposed to tumor necrosis factor- related apoptosis-inducing ligand. *Cancer Res* 2000; 60: 6259-65.
- een snel toegenomen aantal tumoren geïdentificeerd die een rol spelen bij de gevoeligheid van tumoren voor chemotherapie. De klinische hypothesen over de mechanismen verantwoordelijk voor het behoud van tumoren van resistentie tegen chemotherapie is gebaseerd op het functioneren van deze tumoren om zijn intracellulaire doel te bereiken. Dit kan bijvoorbeeld worden veroorzaakt worden door het sneller uitpompken van medicatie uit de cel of een toegenomen ontgiffing van medicatie. Ook kan een sterker vermogen van de tumor om DNA-schade te repareren of DNA- crosslinks te verdragen leiden tot een grotere ongevoeligheid voor alle typen chemotherapie. Met name het ontstaan van ongevoeligheid voor meerdere, structureel niet verwante soorten chemotherapeutische medicatie (multidrug resistentie) is algemeen bekend. De zijn verschillende transmembran transporters geïdentificeerd, die in staat zijn dit type resistentie te veroorzaken. De meest bekende zijn het P-glycoproteïne (P-gp) en het Multidrug Resistance Proteïne 1 (MRP1). Alhoewel een relatie tussen de verhoogde aanwezigheid van deze eiwitten en multidrug resistentie in tumor cellijnen en in dierecellen is gevonden, blijkt het niet goed mogelijk om deze relatie aan te toonen in de klinische praktijk. Bovendien blijken strategieën, die gericht zijn op het neutraliseren van deze resistentie eiwitten tot nu toe niet te leiden tot een beter behandelingsresultaat bij patiënten met solide tumoren.
- De laatste jaren wordt steeds duidelijker dat de meeste chemotherapeutische middelen effectief zijn door het intrinsieke vermogen van de tumorcel om zichzelf te vernietigen op het moment dat er onherstelbare DNA schade is opgetreden. Dit mechanisme, waarbij de tumorcel als de activering van een ingewikkelde intracellulaire route te grote pest, wordt apoptose genoemd. Het onvermogen van een tumorcel om in apoptose te gaan wordt veroorzaakt door chemotherapeutische